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Negative affect shared with siblings is associated with structural brain network efficiency and loneliness in adolescents

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Highlights

- Sibling-average positive affect is negatively associated with local network efficiency
- Sibling-average negative affect is positively associated with global and local network efficiency
- Network efficiency negatively mediates the association between sibling-average negative affect and loneliness

Abstract

Loneliness has a strong neurobiological basis reflected by its specific relationships with structural brain connectivity. Critically, affect traits are highly related to loneliness, which shows close association with the onset and severity of major depressive disorder. This diffusion imaging study was conducted on a sample of adolescent siblings to examine whether positive and negative affect traits were related to loneliness, with brain network efficiency playing a mediating role. The findings of this study confirmed that both global and average local efficiency negatively mediated the association between low positive affect and high negative affect and loneliness, and the mediation was more sensitive to sibling-shared affect traits. The findings have important implications for interventions targeted at reducing the detrimental impact of familiar negative emotional experiences and loneliness.

Keywords: Network Efficiency; Loneliness; Diffusion MRI; Siblings; Adolescence.

Introduction

Loneliness is a subjective feeling of dissatisfaction that is aroused when a person's actual social relationships are deemed inadequate in light of his or her social needs (Peplau and Perlman, 1982). Loneliness is becoming a societal problem as there is an increasing number of people suffering from prolonged loneliness that contributes to high morbidity and mortality (Holt-Lunstad et al., 2015). Loneliness is also regarded as one of the key characteristics in depressive patients and could predict the onset and severity of major depressive disorder (Cacioppo et al., 2010, 2015b).

While feeling lonely at times is common, some individuals are more prone to perceive loneliness than others. Previous literature has suggested that affect traits could be strong predisposing factors related to loneliness (Asendorpf and van Aken, 2003). For instance, negative affect is proposed to hamper an individual's perception of inclusion in social situations (Jones et al., 1982), whereas positive affect is suggested to help broaden one's social resources (Fredrickson, 1998; Diener and Seligman, 2002), indicating a close relationship between affect traits and loneliness. Additionally, trait neuroticism, which is linked with high negative affect, and trait extroversion, which is linked with high positive affect, have been found to mediate the relationship between loneliness and brain structures in the prefrontal cortex (Kong et al., 2015). The neuropsychological mechanism of how affect traits could be strongly influential to an individual's loneliness is yet to be understood, but recent neuroimaging literature on loneliness has provided insights into brain network configuration as a crucial explanatory factor of loneliness.

Loneliness has heavy neural underpinnings. This is mainly supported by the theoretical framework postulating that the brain is evolved to facilitate survival by influencing an individual's perception of social relationships and her processing of social emotional information through neural mechanisms (Cacioppo et al., 2014). Some of the brain regions, the "social brain", are particularly relevant, such as the medial prefrontal cortex (mPFC), in addition to the anterior cingulate cortex (ACC), temporo-parietal junction, and anterior temporal regions (Frith, 2007). Functional MRI (fMRI) studies have also found that lonelier individuals have less activation in the ventral striatum when processing pleasant social pictures (Cacioppo et al., 2009) and could differentiate negative social stimuli more quickly by activating the fusiform gyrus, ACC, and other occipital areas, implying their hypervigilance to social and emotional content (Cacioppo et al., 2015a). Crucially, further evidence has revealed that brain connectivity bridging these regions is

closely associated with loneliness (Tian et al., 2014, 2017; Nakagawa et al., 2015; Lan et al., 2016; Wong et al., 2016; Layden et al., 2017), with less connected white matter fiber bundles related to higher loneliness in adults (Tian et al., 2014; Nakagawa et al., 2015; Wong et al., 2016).

Extending from the existing research, the current study focused on investigating whether structural brain network could explain the effects of positive and negative affect traits on loneliness using diffusion MRI (dMRI). We focused on adolescents because adolescence is a life stage in which individuals are particularly vulnerable to loneliness. It is also reported previously that higher loneliness in adolescents may interfere with structural brain connectivity (Wong et al., 2018). Structural brain network efficiency could be particularly critical to adolescents' feelings of loneliness as the network efficiency of the adolescents is highly related to their cognitive functioning (Koenis et al., 2015, 2018). Therefore, we examined whether adolescents' affect traits were related to the global and local network efficiencies of their structural brain network and their feelings of loneliness. Moreover, we have utilized a sibling-control design and conducted our analyses on a sample of adolescent sibling pairs. This design has the advantage of delineating the causes of the observed associations into individual factors versus familial factors, with the latter being shared between the siblings (Carlin et al., 2005). The inclusion of sibling pairs allowed us to tease apart individual (i.e., varied between siblings) and familial (i.e., shared between siblings) aspects of affect variance and their respective relationships with the structural brain network and loneliness. Based on the existing literature outlined above, we hypothesized that **(1)** affect traits would be associated with both global network efficiency and local network efficiency in brain areas involved in social and affective processes, such as the mPFC, and **(2)** the efficiency measures would be related to loneliness.

Experimental procedures

Participants

Adolescent sibling pairs from the “Children of 1997” birth cohort (Schooling et al., 2012) or identified by word of mouth were contacted. Only those without any reported learning difficulties or psychological or neurological diseases were recruited. A final sample of 40 adolescents with a mean age of 17.8 years and mean IQ of 102.8 were recruited (20 same-sex sibling pairs; age range: 15–19 years; Male: 9 pairs; Female: 11 pairs) (**Table 1**). All participants completed the psychometric assessments and underwent an MRI scanning session on the same day, during which dMRI data were collected.

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The study was carried out in accordance with their guidelines and regulations and the Declaration of Helsinki. Signed informed consent was obtained from all subjects (if ≥ 18 years old) or their guardians (if < 18 years old).

Behavioral measures

Loneliness: The 20-item UCLA Loneliness Scale was used to measure the subjects’ loneliness levels (Russell, 1996). It has been reliably replicated in a similar age group and is particularly sensitive to people’s subjective loneliness feelings (Hamid and Lok, 2000). Participants were asked to indicate how often each of the statements was descriptive of them. For instance, there were statements such as, “I feel in tune with the people around me”, “My social relationships are superficial”, and “I can find companionship when I want it”.

Positive and negative affect: We also assessed positive and negative affect traits of all participants using the 20-item Chinese Affect Scale (Hamid and Cheng, 1996), an adaptation of the Positive and Negative Affect Schedule (Watson et al., 1988) on the Chinese population. The scores of affect traits obtained from the scale have stable test-retest reliability, and its psychometric properties are confirmed to be valid (Hamid and Cheng, 1996). The outcome measures were scores on positive affect and negative affect traits. Importantly, participants were asked to indicate to what extent they reacted to each of the items *in general* to capture their affect traits but not states. For instance, items of positive affect included words such as “Excited” and “Active”, and items of negative affect included words such as “Nervous” and “Upset”.

Additional covariates: Participants’ age, gender, and IQ scores as measured with the Test of

Nonverbal Intelligence (TONI, 3rd edition) (Brown, 2003) were also collected.

MRI data acquisition and preprocessing

The dMRI data were acquired with a 3.0T Philips scanner with an 8-channel head coil. For each subject, the dMRI data were acquired with a non-diffusion-weighted image (b_0) with b -values = 1000 and 2000 s/mm^2 using the following parameters: TR = 6,600 ms, TE = 81 ms, FOV = 230×230 mm, voxel size = $2.4 \times 2.4 \times 2.7$ mm, flip angle = 90° , and axial acquisition. The number of diffusion sampling directions for b -values was both 32.

To avoid confounding from motion artifacts, the dMRI acquisition for each subject was monitored and the subject was rescanned if we observed any artifacts. The dMRI data acquired were corrected for eddy current distortion by registering each volume of the subjects' dMRI data to their b_0 image using *eddy_correct* in FSL (Jenkinson et al., 2012). The dMRI data were again inspected and then reconstructed with the generalized q-sampling imaging approach using DSI Studio (Yeh et al., 2010), with a diffusion sampling length ratio of 1.2. Deterministic fiber tracking with whole-brain seeding of 1,000,000 fiber streamlines was performed on each subject. An angular threshold of 45 degrees and a step size of 0.1 mm were adopted to minimize overshoots in highly curved tracts (Jeurissen et al., 2019). The anisotropy threshold was set at 0.1 and tracks shorter than 10 mm or longer than 500 mm were discarded to avoid spurious structural connectivity.

Construction of structural brain network

Each participant's structural brain network was constructed in the subject space using the Automated Anatomical Labeling (AAL) atlas. Because the regions defined in the original AAL atlas were relatively large in size, an n -cut random parcellation scheme was adopted (de Reus and van den Heuvel, 2013) to further parcellate the AAL atlas into 868 nodal regions of smaller and similar sizes (Mean = 213 voxels, SD = 45.0 voxels), avoiding the potential confounding influence of volumetric differences in the nodes (Hagmann et al., 2008). The regions were then nonlinearly registered to each participant's anisotropy map. The weights of the edges of the network matrices were defined by the number of tracked fiber streamlines passing through pairs of nodal regions, normalized by the maximum number of tracked fiber streamlines in each participant. The approach of using volume-based parcellation with higher spatial resolution in network construction has been

suggested to be reliable (Zhao et al., 2015).

Network efficiency of structural brain network

The network efficiency measures could inform on the segregation and integration of the structural brain network and quantify how efficiently the brain exchanges information. The threshold for the structural connectivity matrix of each participant was established across a density range of 0.01-0.05 in steps of 0.01. This density range was chosen to ensure that none of the participants' connectivity matrices would be disconnected by evaluating the backbone of their connectivity matrices at each density. The area under the curve (AUC) of the network efficiency measures across the range was calculated for further analyses and has the advantage of reducing potential biased findings driven by different network densities across participants. At the global level, we focused on **(I)** global efficiency that captures overall network integration and quantifies how efficiently information is exchanged in the global network. We also focused on the **(II)** local efficiency that captures the efficiency of information transfer in the direct neighborhood of a specific node (Bullmore and Sporns, 2012). While reliability of task fMRI measures could be of concern (Zuo et al., 2019), the network efficiency measures are among the network metrics with moderate to good levels of test-retest reliability (Zhao et al., 2015; Xing and Zuo, 2018).

For a network with n number of nodes and l number of edges with edge-wise connection weights w_{ij} between nodes i and j , the strength (k) of node i is the sum of connection weights connecting to node i and is defined by **Equation 1**:

$$k = \sum w_{ij} \dots \dots \dots (1)$$

The global efficiency (E_G) of the network is the average inverse shortest weighted path in the network and is defined by **Equation 2**:

$$E_G = \frac{1}{n} \sum \frac{\sum (d_{ij})^{-1}}{n-1} \dots \dots \dots (2)$$

where d_{ij} is the shortest weighted path length between nodes i and j .

The local efficiency (E_L) of node i is defined similarly to global efficiency but is computed based on the neighbors of node i and is defined by **Equation 3**:

$$E_L = \frac{1}{2n} \sum \frac{\sum (w_{ij} w_{ih} [d_{jh}]^{-1})^{\frac{1}{3}}}{k(k-1)} \dots \dots \dots (3)$$

where nodes j and h are not node i .

Statistical analyses

Linear regression analyses were performed to delineate whether affect traits could statistically predict the efficiency measures of the structural brain network in adolescents and whether such associations were caused by individual or familial factors that were shared between the siblings. These were achieved by setting up the regression models in the form of **Equation 5** (Carlin et al., 2005):

$$y = \beta_0 + \beta_w(x_{pq} - \bar{x}_q) + \beta_B\bar{x}_q \dots\dots\dots(5)$$

where x_{pq} is the value of x (i.e., scores in affect trait) of subject p of the sibling pair q and \bar{x}_q is the mean value of x of the two participants of the sibling pair q . The significance of the coefficient b_w of the deviation term (i.e., $x_{pq} - \bar{x}_q$) infers the contribution of individual factors to the relationship between x (i.e., scores in affect trait) and y (i.e., structural brain network efficiency measures), while the variances explained by familial factors that were shared between the siblings were accounted for by the average term with the coefficient b_B .

Using this regression model (**Equation 5**), we separated the contribution of individual factors from that of familial factors to the associations between affect traits and structural brain network efficiency. For instance, we could be more confident in whether the observed associations would be more related to unique individual factors capturing the difference within a sibling pair, versus familial factors, such as maternal factors, similar genetic compositions, family setting, or socioeconomic status. The associations between structural network efficiency and loneliness were analyzed using linear regression. We then carried out mediation analyses to assess the direct and indirect associations between affect traits and loneliness, and whether the structural brain network efficiency measures mediated the indirect associations. The indirect effects were estimated through Sobel tests.

Bonferroni correction for multiple comparisons was implemented when analyzing the local efficiency, and White robust standard errors corrected for degrees of freedom were calculated to account for the heteroscedasticity of residuals in the regression analyses. Unstandardized regression coefficients are reported for illustrative purposes, and significance was inferred when $p < 0.05$. All the analyses were controlled for age, gender, and IQ and were performed in MATLAB.

Results

Demographics and sample characteristics

No significant difference in positive affect, negative affect or nonverbal IQ was observed between the adolescent siblings ($p > 0.05$) (**Table 1**). It was found that age ($b = 2.9895$, $p = 0.0200$), sibling-average positive affect ($b = -0.4983$, $p = 0.0248$), and individual negative affect ($b = 0.7538$, $p = 0.0397$) were associated with loneliness.

Associations of affect traits and structural brain network efficiency

We first investigated how positive and negative affect traits were related to the structural brain network of the adolescents. For both affect traits, no significant associations were found between individual positive or negative affect and the global efficiency, average local efficiency, or local efficiency of any nodes ($p > 0.05$). On the contrary, sibling-average positive affect was negatively associated with the local efficiency of regions in the superior parietal lobule and posterior cerebellar lobe ($b \leq -0.4060 \times 10^{-4}$, $p \leq 0.0145$) (**Figure 1A**). Sibling-average negative affect was positively associated with global efficiency ($b = 0.1982 \times 10^{-4}$, $p < 0.001$), average local efficiency ($b = 0.1982 \times 10^{-4}$, $p < 0.001$), and local efficiency of regions mainly in the prefrontal cortex, insula, fusiform gyrus and posterior cerebellar lobe ($b \geq 3.3306 \times 10^{-5}$, $p \leq 0.0496$) (**Figure 1B**) (**Table 2**).

Associations of structural brain network efficiency and loneliness

We then investigated whether structural brain network was related to loneliness in adolescents, controlling for their affect traits in addition to the covariates. It was found that global efficiency ($b = -1.5694 \times 10^{-4}$, $p = 0.0159$), average local efficiency ($b = -1.0585 \times 10^{-4}$, $p = 0.0066$), and local efficiency of regions in the hippocampal, caudate nucleus, and posterior cerebellar areas ($b \leq -5.0889 \times 10^{-5}$, $p \leq 0.0467$) were negatively associated with loneliness (**Figure 1C**) (**Table 3**).

Mediation of structural brain network efficiency

To elucidate whether structural brain networks in adolescents had a mediation role and might explain the associations between affect traits and loneliness, we tested whether the network efficiency measures might be mediators of the associations between positive and negative affect

traits and loneliness. We found that both global efficiency ($b = -0.3110$, $p = 0.0260$) (**Figure 2A**) and average local efficiency ($b = -0.3381$, $p = 0.0164$) (**Figure 2B**) of the structural brain network would negatively mediate the association of sibling-average negative affect and loneliness. The direct effects between sibling-average negative affect and loneliness after being mediated by global efficiency ($b = 0.3803$, $p = 0.1802$) and average local efficiency ($b = 0.4074$, $p = 0.1434$) were not significant.

We also tested whether loneliness mediated the associations between affect traits and the network efficiency measures, and no significant mediation effects were observed ($p > 0.05$).

Discussion

In this study, we found that low positive affect and high negative affect shared with siblings in adolescence was associated with increased network efficiency in areas including the posterior cerebellum lobe. High negative affect shared with siblings was also associated with increased network efficiency in the prefrontal cortex including the mPFC, while increased network efficiency of the posterior cerebellum lobe was related to low loneliness. Confirmed by mediation analyses, the overall network efficiency of adolescents' brains appeared to remediate the effect of negative affect shared with siblings on loneliness.

Previous research has found that affect traits and regulation are related to the prefrontal-limbic circuitries, with the lateral and mPFC having a regulatory functional role (Wu et al., 2018). The mPFC is heavily implicated in social cognitive and affective functions (Bzdok et al., 2013) and may also be involved in attention control functions through connecting with the cognitive control network (Eickhoff et al., 2016). The cerebellum is also suggested to be critical to affective processing and regulation, such that damage to the cerebellum would lead to deficits in disinhibition and blunted affect (Schmahmann and Sherman, 1998). Specifically, the posterior cerebellar lobules are associated with cognitive control (Van Overwalle et al., 2014), and the cerebellum coordinates behaviors in response to incoming information, as well as contributing to general cognitive and emotion control (D'Angelo and Casali, 2013). In this study, we found that low positive affect and high negative affect shared with siblings were associated with increased local efficiency in the posterior cerebellar lobe. Furthermore, shared high negative affect was associated with increased local efficiency in the prefrontal cortex, including the mPFC. Local efficiency is interpreted as reflecting the local information-processing capacity of a network (Bullmore and Sporns, 2012), and the network efficiency of the adolescents was found to be highly related to their cognitive functioning (Koenis et al., 2015, 2018). It is thus possible that the structural brain network in adolescents might be an important protective factor against the negative impact of affect traits. Intriguingly, the protective mechanism appeared to be principally concerned with familial factors shared within sibling pairs, rather than individual factors. This might mean that the low positive and high negative affect traits attributed to unique individual factors would have greater impact (due to lack of protective factor), or alternatively might suggest that adolescents' brains are more sensitive to familiar emotional experiences as evidenced by their sensitivity and vulnerability to social influence (Blakemore and Mills, 2014; Wols et al., 2015).

Affect traits are strongly related to loneliness (Asendorpf and van Aken, 2003), and both positive and negative affect traits have been proposed to mediate the individual's perception of inclusion in social situations via different psychological pathways (Jones et al., 1982; Fredrickson, 1998; Diener and Seligman, 2002). Previous research has consistently suggested that negative affect is a significant contributor to the feeling of loneliness (Marcus and Askari, 1999), and that lonelier individuals usually have poor emotion regulation (Hawkley et al., 2009). Here, we have further shown that the higher local efficiency in the posterior cerebellum lobe and caudate nucleus was related to lower loneliness. As discussed earlier, posterior cerebellar lobules are associated with cognitive control (Van Overwalle et al., 2014) and contribute to general emotion control (D'Angelo and Casali, 2013). The posterior cerebellar lobe often activates in mentalization and mirroring tasks and provides general cognitive support for complicated social processes (Van Overwalle et al., 2014). In line with the current findings, it could be that increased posterior cerebellar efficiency is an adaptive mechanism that compensates for the possible deficiencies in social and affective functions that underlie lonelier adolescents. In addition, the role of the caudate nucleus is part of the reward circuitry in processing social rewards (Acevedo et al., 2012). Our current findings could not provide definitive evidence on which neural mechanisms might underlie the adolescents' proneness to loneliness, but the negative mediation effects via increased global and average local efficiency in comparison to the direct effects between shared negative affect and loneliness might further support our postulation that the structural brain network in adolescents might be an important protective factor against the influence of affect traits on loneliness. It is possible that a more efficient brain network could support better cognitive functioning in adolescents (Koenis et al., 2015, 2018), helping them to regulate the influence from negative emotional experience.

One strength of the current study is that it established the mediation role of structural network efficiency on the influence of affect traits on adolescents' loneliness. However, one main limitation was the restricted age range of the participants. We have recruited only adolescents in this dMRI study. Without another age group for comparison, we were not able to confirm whether the mediation effects of the structural brain network in adolescents were similar to/different from those in adults. This prevented us from making inferences regarding the generalizability of our findings. Moreover, it is worth emphasizing that we were interested in the statistical prediction of affect traits on structural brain network efficiency and loneliness which was confirmed by our

regression analyses, but we could not infer any psychobiological causality in the associations based on the current cross-sectional design. Furthermore, we have attempted to increase our understanding and the explanatory power of the associations by using regression models that could delineate potential contributions of individual and familial factors. However, it was not possible for us to identify the specific individual and familial factors that contributed the most to the results. The tentative explanations we discussed above should be interpreted with caution, and they should be validated by future research with more specific focus. Moreover, we measured the affect traits using the Chinese Affect Scale (Hamid and Cheng, 1996), by explicitly asking our participants to respond based on their general affective style. However, it has been argued that this scale may not be ideal for measuring affect traits, and future research may validate our findings using other trait affect scales. Finally, we admit that the reliability of network measures is highly dependent on the density of the network and the measure chosen. In this study, we applied a range of density thresholds during network construction and performed analyses on the AUC of the network measures in an attempt to reduce the potential confounds from the inter-subject variations of network density and the instability of network measures at a particular density. Future studies could consider different network construction strategies to validate the current findings.

Conclusions

The current study revealed the protective role of structural brain network efficiency, both globally and locally, on the impact of low positive and high negative affect traits shared with siblings on loneliness in adolescents. Our findings have important implications for interventions targeted at reducing the detrimental impact of familiar negative emotional experiences and loneliness, for which brain efficiency is crucial.

References

- Acevedo BP, Aron A, Fisher HE, Brown LL (2012) Neural correlates of long-term intense romantic love. *Soc Cogn Affect Neurosci* 7:145–159.
- Asendorpf JB, van Aken MAG (2003) Personality-relationship transaction in adolescence : core versus surface personality characteristics. *J Pers* 71:629–666.
- Blakemore S-J, Mills KL (2014) Is adolescence a sensitive period for sociocultural processing? *Annu Rev Psychol* 65:187–207.
- Brown L (2003) Test of Nonverbal Intelligence: A language-free measure of cognitive ability. In: *Handbook of nonverbal assessment.*, pp 191–221.
- Bullmore E, Sporns O (2012) The economy of brain network organization. *Nat Rev Neurosci* 13:336–349.
- Bzdok D, Langner R, Schilbach L, Engemann DA, Laird AR, Fox PT, Eickhoff SB (2013) Segregation of the human medial prefrontal cortex in social cognition. *Front Hum Neurosci* 7:232.
- Cacioppo JT, Hawkley LC, Thisted RA (2010) Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychol Aging* 25:453–463.
- Cacioppo JT, Norris CJ, Decety J, Monteleone G, Nusbaum H (2009) In the eye of the beholder : individual differences in perceived social isolation predict regional brain activation to social stimuli. *J Cogn Neurosci* 21:83–92.
- Cacioppo S, Capitanio JP, Cacioppo JT (2014) Toward a neurology of loneliness. *Psychol Bull* 140:1464–1504.
- Cacioppo S, Balogh S, Cacioppo JT (2015a) Implicit attention to negative social, in contrast to nonsocial, words in the Stroop task differs between individuals high and low in loneliness: evidence from event-related brain microstates. *Cortex* 70:213–233.
- Cacioppo S, Grippo J, London S, Goossens L, Cacioppo JT (2015b) Loneliness: Clinical Import and Interventions. *Perspect Psychol Sci* 10:238–249.
- Carlin JB, Gurrin LC, Sterne JA, Morley R, Dwyer T (2005) Regression models for twin studies: a critical review. *Int J Epidemiol* 34:1089–1099.
- D’Angelo E, Casali S (2013) Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. *Front Neural Circuits* 6:116.

- de Reus MA, van den Heuvel MP (2013) Rich club organization and intermodule communication in the cat connectome. *J Neurosci* 33:12929–12939.
- Diener E, Seligman MEP (2002) Very happy people. *Psychol Sci* 13:81–84.
- Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L (2016) Functional Segregation of the Human Dorsomedial Prefrontal Cortex. *Cereb Cortex* 26:304–321.
- Fredrickson BL (1998) What good are positive emotions? *Rev Gen Psychol* 2:300–319.
- Frith CD (2007) The social brain? *Philos Trans R Soc Lond B Biol Sci* 362:671–678.
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6:e159.
- Hamid PN, Cheng S-T (1996) The development and validation of an index of emotional disposition and mood state: The Chinese Affect Scale. *Educ Psychol Meas* 56:995–1014.
- Hamid PN, Lok DPP (2000) Loneliness in Chinese Adolescents: A Comparison of Social Support and Interpersonal Trust in 13 to 19 Year Olds. *Int J Adolesc Youth* 8:45–63.
- Hawkey LC, Thisted RA, Cacioppo JT (2009) Loneliness predicts reduced physical activity: cross-sectional & longitudinal analyses. *Heal Psychol* 28:354–363.
- Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D (2015) Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci* 10:227–237.
- Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM (2012) FSL. *Neuroimage* 62:782–790.
- Jeurissen B, Descoteaux M, Mori S, Leemans A (2019) Diffusion MRI fiber tractography of the brain. *NMR Biomed* 32:e3785.
- Jones WH, Hobbs SA, Hockenbury D (1982) Loneliness and social skill deficits. *J Pers Soc Psychol* 42:682–689.
- Koenis MMG, Brouwer RM, Swagerman SC, van Soelen ILC, Boomsma DI, Hulshoff Pol HE (2018) Association between structural brain network efficiency and intelligence increases during adolescence. *Hum Brain Mapp* 39:822–836.
- Koenis MMG, Brouwer RM, van den Heuvel MP, Mandl RCW, van Soelen ILC, Kahn RS, Boomsma DI, Hulshoff Pol HE (2015) Development of the brain's structural network efficiency in early adolescence: A longitudinal DTI twin study. *Hum Brain Mapp* 36:4938–4953.

- Kong X, Wei D, Li W, Cun L, Xue S, Zhang Q, Qiu J (2015) Neuroticism and extraversion mediate the association between loneliness and the dorsolateral prefrontal cortex. *Exp brain Res* 233:157–164.
- Lan C-C, Tsai S-J, Huang C-C, Wang Y-H, Chen T-R, Yeh H-L, Liu M-E, Lin C-P, Yang AC (2016) Functional connectivity density mapping of depressive symptoms and loneliness in non-demented elderly male. *Front Aging Neurosci* 7:251.
- Layden EA, Cacioppo JT, Cappa SF, Dodich A, Falini A, Canessa N (2017) Perceived social isolation is associated with altered functional connectivity in neural networks associated with tonic alertness and executive control. *Neuroimage* 145:58–73.
- Marcus DK, Askari NH (1999) Dysphoria and interpersonal rejection: a social relations analysis. *J Soc Clin Psychol* 18:370–384.
- Nakagawa S, Takeuchi H, Taki Y, Nouchi R, Sekiguchi A, Kotozaki Y, Miyauchi CM, Iizuka K, Yokoyama R, Shinada T, Yamamoto Y, Hanawa S, Araki T, Hashizume H, Kunitoki K, Sassa Y, Kawashima R (2015) White matter structures associated with loneliness in young adults. *Sci Rep* 5:17001.
- Peplau LA, Perlman D (1982) Perspective on loneliness. In: *Loneliness: A Sourcebook of Current Theory, Research and Therapy.*, pp 1–20.
- Russell DW (1996) UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J Pers Assess* 66:20–40.
- Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. *Brain* 121:561–579.
- Schooling CM, Hui LL, Ho LM, Lam T-H, Leung GM (2012) Cohort profile: “Children of 1997”: a Hong Kong Chinese birth cohort. *Int J Epidemiol* 41:611–620.
- Tian Y, Liang S, Yuan Z, Chen S, Xu P, Yao D (2014) White matter structure in loneliness: preliminary findings from diffusion tensor imaging. *Neuroreport* 25:843–847.
- Tian Y, Yang L, Chen S, Guo D, Ding Z, Tam KY, Yao D (2017) Causal interactions in resting-state networks predict perceived loneliness. *PLoS One* 12:1–15.
- Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M (2014) Social cognition and the cerebellum: A meta-analysis of over 350 fMRI studies. *Neuroimage* 86:554–572.
- Watson D, Clark LA, Tellegen A (1988) Positive and negative affect schedule (PANAS). *J Pers Soc Psychol* 54:1063–1070.

- Wols A, Scholte RHJ, Qualter P (2015) Prospective associations between loneliness and emotional intelligence. *J Adolesc* 39:40–48.
- Wong NML, Liu H-L, Lin C, Huang C-M, Wai Y-Y, Lee S-H, Lee TMC (2016) Loneliness in late-life depression: structural and functional connectivity during affective processing. *Psychol Med* 46:2485–2499.
- Wong NML, Yeung PPS, Lee TMC (2018) A developmental social neuroscience model for understanding loneliness in adolescence. *Soc Neurosci* 13:94–103.
- Wu J, Geng X, Shao R, Wong NML, Tao J, Chen L, Chan CCH, Lee TMC (2018) Neurodevelopmental changes in the relationship between stress perception and prefrontal-amygdala functional circuitry. *NeuroImage Clin* 20:267–274.
- Xing XX, Zuo XN (2018) The anatomy of reliability: a must read for future human brain mapping. *Sci Bull* 63:1606–1607
- Yeh F-C, Wedeen VJ, Tseng WI (2010) Generalized q-Sampling Imaging. *IEEE Trans Med Imaging* 29:1626–1635.
- Zhao T, Duan F, Liao X, Dai Z, Cao M, He Y, Shu N (2015) Test-retest reliability of white matter structural brain networks: a multiband diffusion MRI study. *Front Hum Neurosci* 9:1–18.
- Zuo XN, Xu T, Milham MP (2019) Harnessing reliability for neuroscience research. *Nat Hum Behav* 3:768–771.

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Declarations of Interest

None.

Table 1. Demographics and characteristics of the adolescents and their siblings

	Adolescents	Siblings	<i>t</i>-statistic	<i>p</i>-value
	(N = 20)	(N = 20)		
<i>Characteristics</i>				
Age (years)	17.8 (1.21)	17.8 (1.21)	-	-
Gender	9:11	9:11	-	-
TONI quotient	103.1 (15.52)	102.4 (13.02)	0.244	0.810
<i>Psychometrics</i>				
Loneliness	34.9 (9.48)	44.0 (8.11)	-	-
Positive Affect	21.8 (9.54)	22.7 (8.69)	0.525	0.606
Negative Affect	10.8 (8.26)	12.6 (7.90)	0.941	0.358

TONI = Test of Nonverbal Intelligence; Means along with Standard Deviations in parentheses are shown, except for gender.

Table 2. Significant associations between affect traits and area under the curve of structural brain network efficiency measures

		Laterality	Linear Regression			
			<i>b</i>	<i>se</i>	<i>t</i>	<i>p</i>
<u>Sibling-average positive affect</u>						
Local efficiency						
Superior parietal lobule	R		-0.000041	0.000008	-5.059	0.015
Cerebellum crus II	R		-0.000074	0.000014	-5.284	0.008
Cerebellum VIIb	L		-0.000045	0.000009	-5.076	0.014
Cerebellum VIII	L		-0.000062	0.000009	-6.879	0.000
			-0.000050	0.000009	-5.578	0.003
Cerebellum IX	R		-0.000044	0.000007	-5.922	0.001
<u>Sibling-average negative affect</u>						
Global efficiency			0.000020	0.0000043	4.567	<0.001
Average local efficiency			0.000032	0.0000008	4.236	<0.001
Local efficiency						
Superior frontal gyrus	L		0.000071	0.000015	4.894	0.023
			0.000062	0.000013	4.729	0.038
Superior frontal gyrus (orbital)	L		0.000057	0.000011	5.179	0.010
	R		0.000052	0.000011	4.720	0.039
Middle frontal gyrus	L		0.000081	0.000013	6.113	0.001
	L		0.000091	0.000017	5.242	0.009
Middle frontal gyrus (orbital)	R		0.000064	0.000013	5.005	0.017
Inferior frontal gyrus (opercular)	L		0.000047	0.000009	5.339	0.006
	L		0.000071	0.000015	4.636	0.050

Inferior frontal gyrus (orbital)	L	0.000066	0.000009	7.319	<0.001
Rolandic operculum	L	0.000050	0.000008	6.421	<0.001
Superior frontal gyrus (medial)	L	0.000068	0.000012	5.668	0.002
Rectus	R	0.000056	0.000009	6.293	<0.001
Insula	L	0.000067	0.000014	4.826	0.029
	R	0.000033	0.000007	4.793	0.031
Superior occipital gyrus	L	0.000059	0.000012	5.010	0.017
Inferior occipital gyrus	R	0.000040	0.000007	5.478	0.004
Fusiform gyrus	R	0.000068	0.000013	5.318	0.007
		0.000101	0.000020	5.081	0.014
		0.000075	0.000014	5.395	0.005
		0.000061	0.000010	5.991	0.001
		0.000056	0.000012	4.834	0.028
Postcentral gyrus	L	0.000065	0.000010	6.190	0.001
		0.000064	0.000011	5.897	0.001
		0.000061	0.000009	6.878	<0.001
Inferior parietal lobule	R	0.000054	0.000011	4.883	0.024
		0.000077	0.000016	4.714	0.039
Middle temporal gyrus	L	0.000056	0.000011	5.263	0.008
Inferior temporal gyrus	L	0.000055	0.000010	5.344	0.006
Cerebellum crus II	L	0.000060	0.000010	6.002	0.001
Cerebellum VI	R	0.000090	0.000019	4.863	0.026

Table 3. Significant associations between area under the curve of structural brain network efficiency measures and loneliness

		Laterality	Linear Regression			
			<i>b</i>	<i>se</i>	<i>t</i>	<i>p</i>
Global efficiency			-15693.63	6153.60	-2.550	0.016
Average local efficiency			-10584.64	3632.60	-2.914	0.007
Local efficiency						
	Hippocampus	R	-6176.74	1269.37	-4.866	0.027
	Parahippocampal gyrus	R	-9071.58	1351.16	-6.714	0.000
	Calcarine fissure	L	-6451.05	1378.75	-4.679	0.047
	Middle occipital gyrus	L	-9116.21	1906.45	-4.782	0.035
	Caudate nucleus	L	-8685.40	1592.75	-5.453	0.005
	Superior temporal gyrus	L	-9700.84	1773.32	-5.470	0.005
		R	-8104.36	1659.35	-4.884	0.026
	Inferior temporal gyrus	L	-5088.92	1013.07	-5.023	0.017
		R	-9301.83	1864.89	-4.988	0.019
	Cerebellum VI	R	-7175.60	1493.85	-4.803	0.033

Figure 1. Associations between affect traits, loneliness, and structural network efficiency measures of significant nodes defined by random parcellation of the original Automated Anatomical Labeling atlas. **(A)** Sibling-average positive affect was negatively associated with the local efficiency of 6 nodes across superior parietal lobule and posterior cerebellar lobe. **(B)** Sibling-average negative affect was positively associated with local efficiency of 31 nodes mainly across the prefrontal cortex, fusiform gyrus and posterior cerebellar lobe. **(C)** Local efficiency of 10 nodes across caudate nucleus and posterior cerebellar areas was negatively associated with loneliness.

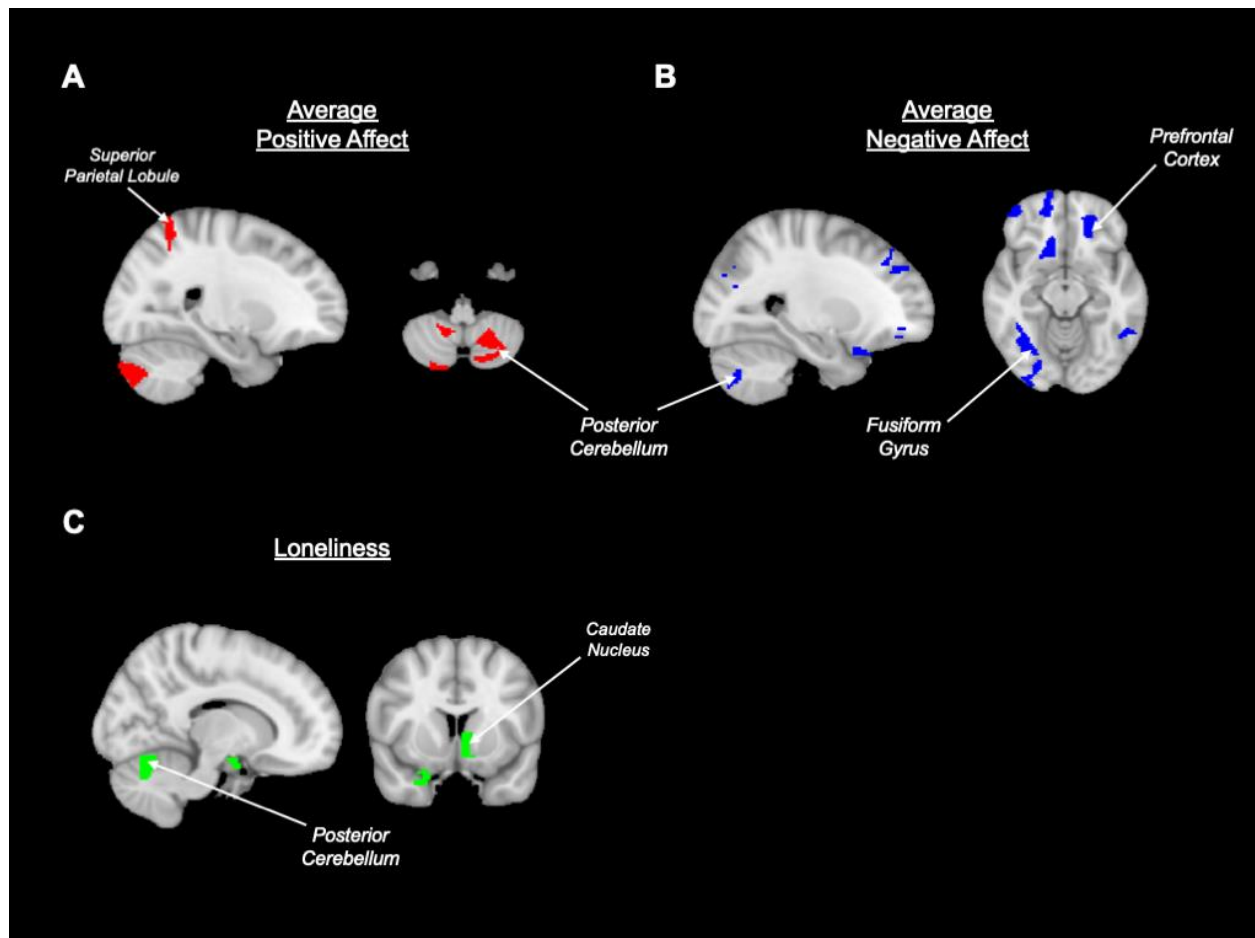


Figure 2. Path diagrams of significant mediating effects of structural network efficiency measures, (A) global efficiency and (B) average local efficiency, on the associations between individual and sibling-average scores of positive and negative affect traits, and loneliness. The unstandardized regression coefficients of the paths are reported. Black arrows denote the significant mediation paths. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

